

Bandolier Extra

People love to click, but hate to scroll. Most of us using the Internet are grateful that there is so much to be found so quickly. But few of us want to read something meaty on a screen. Rather we would like to print it out, and read it sitting in a comfy chair with a cup of tea.

That philosophy was behind the development of *Bandolier Extra* on our Internet site. This has downloadable and printable PDFs of longer content or items specially commissioned, as well as all back copies of *Bandolier* and *IMpAct* (running three months behind). Every week about 7,000-10,000 PDFs are downloaded.

This year, 2003, will see more developments, some of which have been in the planning for a while, and which are being held up for the moment. Look out for an announcement, hopefully in the next few months. Other plans have come to fruition. *Bandolier* has been commissioned to produce pieces for the National electronic Library of Health (NeLH), and new items will appear every month.

Bandolier's Little Book of Pain

Part of the background to the clicking and scrolling argument was requests from readers to produce a book of the Internet site. On the face of it, that's a strange request. The way it was explained to *Bandolier* was that while the Internet was great, many people wanted the comfort of knowing they had a collection of evidence immediately available to them in the form of a book.

As usual, *Bandolier* bowed to reader demand, and the first in what is hoped will be a series appears in April. *Bandolier's Little Book of Pain* pulls together good evidence from systematic reviews and other sources on acute pain, chronic pain, and arthritis, and on complementary therapies and management issues. It also has a light introduction about understanding evidence.

The book is published by Oxford University Press, has 464 pages in a pocket-sized format, and will be available from April 2003 at £19.99 in the UK. It can be ordered from any bookseller, but also from the OUP Internet site, or BMJ books. *Bandolier* will also carry details on its Internet site.

Readers' suggestions for future books are most welcome.

MASTECTOMY VERSUS LUMPECTOMY FOR BREAST CANCER

With early, non-invasive breast cancer, surgery to remove the cancer is usually the treatment of choice. But what type of surgery? Should it be radical – removal of the whole breast – or minimal, removal of the lump and conserving the breast? Randomised trials have been criticised because with small breast cancers follow-up must be for a long time to be sure that differences in recurrence locally or at distant sites are not being missed. Two studies have now reported on 20-year follow-up, and both confirm that lumpectomy plus irradiation gives similar results to radical mastectomy [1,2].

Italian study [1]

Between 1973 and 1980, 701 women with breast cancers with a maximal diameter of 2 cm or less (stage T1) and no palpable nodes and who were younger than 70 years were recruited. They were randomised to radical mastectomy or breast-conserving surgery with complete axillary dissection and postoperative irradiation to the affected breast. From 1976 all patients with positive axillary nodes were additionally given 12 monthly cycles of chemotherapy.

Patients were seen every three months for the first 10 years, and annually thereafter. Annual visits included mammography.

Results

The average age of the women was 51 years, and the median follow up was 20 years. Only three women were lost to follow up. In almost all women the primary cancer was palpable. The two groups of women had similar baseline characteristics for menopausal status, size and site of tumour and axillary node metastases.

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Table 1: Twenty-year results of Italian randomised trial of breast cancer surgery

	Radical mastectomy	Breast-conserving surgery
Number	349	352
Outcome [number, (%)]		
Local recurrence	8 (2.3)	30 (8.6)
Contralateral breast cancer	34 (9.7)	29 (8.3)
Distant metastases	83 (24)	82 (24)
Other primary cancers	30 (8.6)	31 (8.9)
All cause death	152 (44)	156 (44)
Breast cancer death	86 (25)	91 (26)

The results are shown in Table 1. The only significant difference was in the rate of local recurrence, at 2.3% for radical mastectomy and 8.6% for breast-conserving surgery. There was no difference in rates of contralateral breast cancer, distant metastases, other cancers, breast cancer deaths or all-cause mortality.

US study [2]

Between 1976 and 1984 women with breast cancers with a maximal diameter of 4 cm or less and with negative or positive axillary nodes were randomised to radical mastectomy, lumpectomy, or lumpectomy plus breast irradiation.

Results

There were 1,851 women followed up for an average of 20 years. About 60% of women were older than 50 years. The groups had similar baseline characteristics for menopausal status, size and site of tumour and axillary node metastases.

The results are shown in Table 2. The only significant difference was in the rate of local recurrence, at 2.7% for breast-conserving surgery with irradiation but higher for radical mastectomy and lumpectomy alone. There was no difference in rates of contralateral breast cancer, distant

metastases, other cancers, breast cancer deaths or all-cause mortality.

The cumulative incidence of death from any cause in all 1,851 women was 54% at 20 years, and 40% died after a recurrence or diagnosis of cancer in the contralateral breast.

Comment

Results were consistent, with the exception that the Italian study found lower rates of local recurrence with mastectomy, albeit with few actual events. Meta-analyses of trials in breast cancer have found no significant difference between mastectomy and lumpectomy at 10 years.

The finding of these two trials of no important difference at 20 years provides even more confidence that, where appropriate, lumpectomy plus irradiation is safe and effective treatment for early breast cancer.

Remarkable in these trials is the high degree of follow up over 20 years, and the consistency of the results. Together with other evidence that mastectomy does not have any survival advantage over lumpectomy, the lack of superiority of mastectomy over breast-conserving surgery is pretty much nailed down.

The question of which women with breast cancer should be offered which treatment is eloquently addressed in an accompanying article [3]. The thrust of this is that breast-conserving surgery is underused, at least in the USA.

References:

- 1 U Veronesi et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *New England Journal of Medicine* 2002 347: 1227-1232.
- 2 B Fisher et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *New England Journal of Medicine* 2002 347: 1233-1241.
- 3 M Morrow. Rational local therapy for breast cancer. *New England Journal of Medicine* 2002 347: 1270-1271.

Table 2: Twenty-year results of US randomised trial of breast cancer surgery

	Radical mastectomy	Lumpectomy alone	Lumpectomy plus irradiation
Number	589	634	628
Outcome [number, (%)]			
Local recurrence	60 (10)	58 (8.8)	17 (2.7)
Contralateral breast cancer	50 (8.5)	5.6 (8.8)	59 (9.4)
Distant metastases	132 (22)	158 (25)	163 (26)
Other primary cancers	43 (7.3)	32 (5.0)	49 (7.8)
All cause death	371 (63)	408 (64)	391 (62)

TOPICAL AND ORAL TREATMENTS FOR FOOT FUNGAL INFECTIONS

Fungal infections of the foot are remarkably common, affecting about 15% of people in the UK. Topical fungicides, some available without prescription from chemists, are the first treatment option. When they fail, oral fungicides can be tried. Two systematic reviews tell us how effective these are.

Systematic reviews

Both systematic reviews [1,2] had a wide search strategy for randomised trials. As well as at least 10 electronic databases, several journals were hand searched and companies and schools of podiatry in the UK were asked for unpublished trials. For skin infections, only trials that used microscopy and culture were included. The outcome was cure rate at follow up from the reported mycological results, with negative results on microscopy and no growth on culture.

Results for topical azoles

Twelve trials with more than 10 patients in both treatment groups compared azoles with placebo (Figure 1). Usually treatment was for four to six weeks, and follow up for four to 10 weeks.

With azole, 407/480 (85%) patients were cured compared with 173/438 (39%) with placebo. The relative benefit was 2.1 (95% confidence interval 1.9 to 2.4). The number needed to treat to affect one cure compared with placebo was 2.2 (2.0 to 2.5).

Six trials had more than 50 patients, with 74% of the patients. The proportions cured with azole and placebo were 83% and 37% respectively. The NNT was 2.2 (1.9 to 2.6).

Figure 2: Topical azoles versus placebo

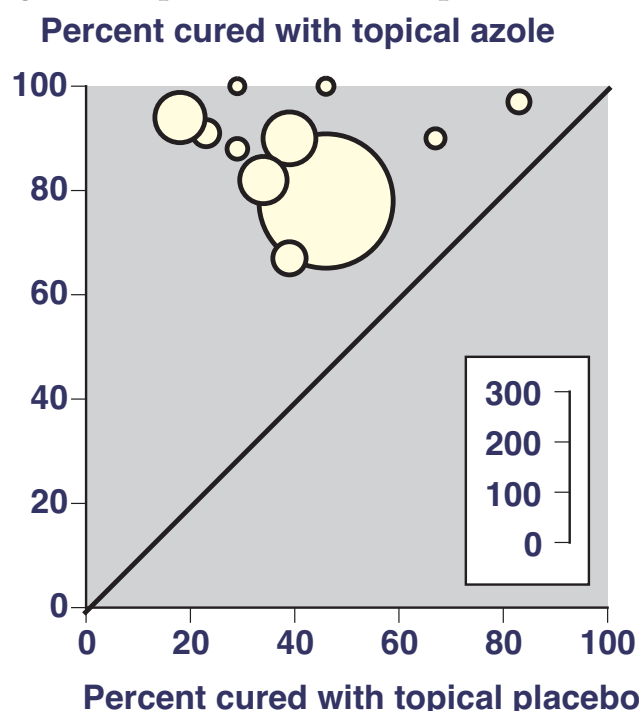
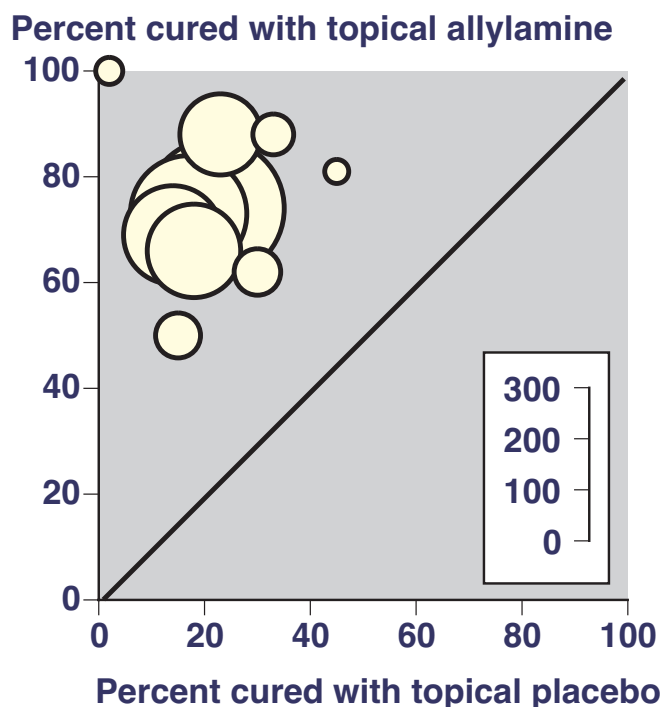


Figure 2: Topical allylamines versus placebo



Results for topical allylamines

Ten trials with more than 10 patients in both treatment groups compared allylamines with placebo (Figure 2). Usually treatment was for one to four weeks, and follow up for six to eight weeks.

With allylamine, 519/706 (74%) patients were cured compared with 139/687 (20%) with placebo. The relative benefit was 3.6 (95% confidence interval 3.1 to 4.2). The number needed to treat to affect one cure compared with placebo was 1.9 (1.7 to 2.1).

Nine trials had more than 50 patients, with 97% of the patients. For these the proportions cured with allylamine and placebo were 73% and 20% respectively. The NNT was 2.2 (1.9 to 2.0).

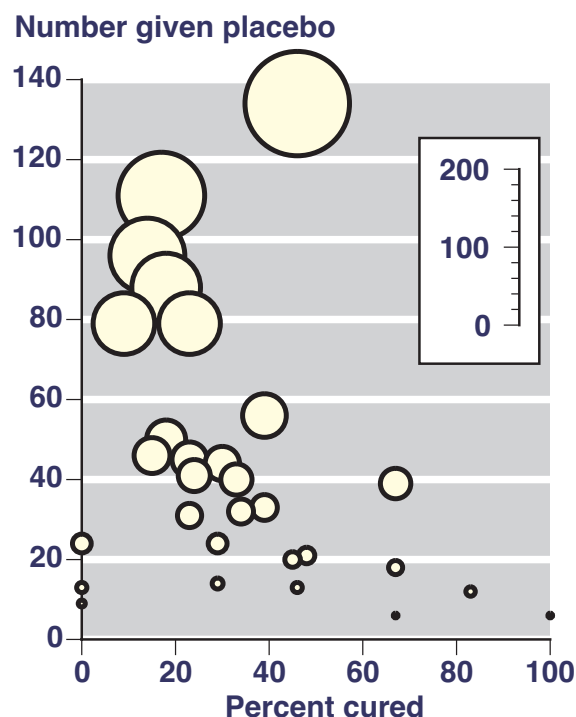
Results for topical undecanoates

Four trials with more than 10 patients in both treatment groups compared undecanoates with placebo. Usually treatment was for four to six weeks, and follow up for six to eight weeks.

With undecanoates, 83/123 (67%) patients were cured compared with 21/81 (26%) with placebo. The relative benefit was 2.7 (95% confidence interval 1.8 to 3.9). The number needed to treat to affect one cure compared with placebo was 2.4 (1.9 to 3.5). All trials had more than 50 patients.

For azoles, allylamines, and undecanoates there was much more variability for the cure rate with placebo in small trials (Figure 3). Including the smallest trials, with only six patients per treatment group, the cure rate varied between 0% and 100%. Overall the rate with topical placebo was 28%.

Figure 3: Response with topical placebo



Results for oral treatments [2]

There were 12 randomised trials, all described as double blind, which evaluated a number of treatments, few of which compared the same treatments. The results as percentage of patients cured for all 24 treatment arms are shown in Figure 4. Higher cure rates were seen for fluconazole and ketoconazole, ahead of terbinafine, itraconazole and griseofulvin.

Two trials, with only 71 patients in total, evaluated terbinafine 250 mg versus griseofulvin 500 mg. Cure rates were 92% and 39% respectively, with a NNT of 1.9 (1.4 to 2.9) for terbinafine compared with griseofulvin.

Four trials, with 339 patients in total, evaluated terbinafine 250 mg versus itraconazole 100 mg. Cure rates were 80% and 65% respectively, with a NNT of 7 (4.2 to 20) for terbinafine compared with itraconazole.

Figure 4: Oral treatments for fungal foot infections (daily doses)

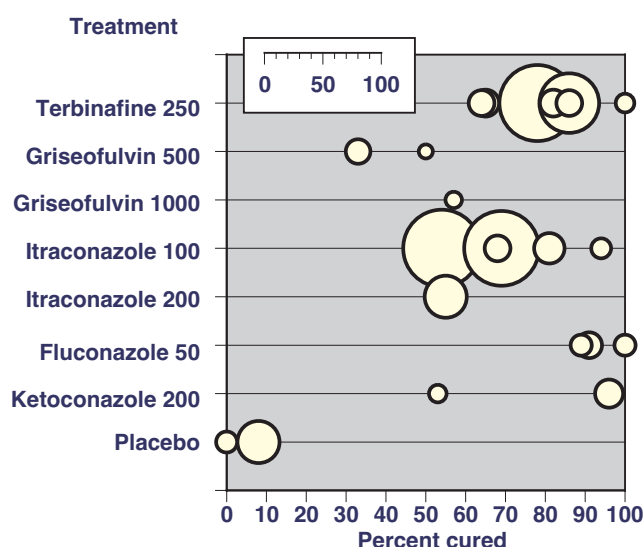


Table 1: Treatments for fungal foot infections compared

Treatment	Cured (number/total)	Percent cured (95% CI)
Topical azoles	407/480	85 (81 to 89)
Oral terbinafine	163/199	82 (76 to 88)
Topical allylamines	519/706	74 (70 to 78)
Topical undecanoate	83/123	67 (59 to 75)
Oral itraconazole	116/178	65 (57 to 73)
Oral griseofulvin	13/33	39 (23 to 55)

Comment and costs

An immediate reflection on these trials is, that for a common complaint, how small was the total number of patients treated, and how small were many of the trials. Admittedly, for topical treatments there were other active-controlled trials, but trials with more than 20 patients per treatment group were the exception.

Both the reviews have a brief discussion about cost effectiveness, based on acquisition costs of medicines and effectiveness from trials. For a number of possible treatments any estimate of the size of the treatment effect is little more than a guess because the numbers are so small.

The best evidence was for topical azoles and allylamines, with 480 and 706 patients. For all others there was information on fewer than 200 patients, and for oral griseofulvin only 33 (Table 1). It is impossible to do useful cost effectiveness work when the limits on knowledge of effectiveness are so profound.

Some of these treatments cost more than others, and some work better than others. Maybe we should ask whether we should use treatments for which there is little information, especially when the evidence we have says they are less effective. Treatments that are more effective will probably cost less in the end, especially when it means patients do not have to come back so often.

In a health service where lack of capacity is the big issue, interventions that relieve the strain on capacity should have a premium to balance against acquisition costs. The second review begins to address this argument for the economic comparison of oral griseofulvin versus oral terbinafine. Even though griseofulvin has a lower acquisition cost, the implication from the trial results is that terbinafine is actually cheaper when a consultation costs more than £25. Given that in some areas of the UK general practitioners are thin on the ground, the traditional cost of a GP visit of about £16 may need revision.

References:

- 1 R Hart et al. Systematic review of topical treatments for fungal infections of the skin and nails of the feet. *BMJ* 1999 319: 79-82.
- 2 SEM Bell-Sayer et al. A systematic review of oral treatments for fungal infections of the skin of the feet. *Journal of Dermatological Treatments* 2001 12: 69-74.

PHYSICIAN STAFFING AND ICU OUTCOMES

A recent theme in *Bandolier* has been reporting studies that looked at staffing levels and outcomes for nurses (*Bandolier* 103 and 106). Both showed that lower nurse staffing levels generally and in the intensive care unit (ICU) led to higher patient mortality, among other outcomes. A new systematic review on physician staffing in the ICU confirms that higher intensity staffing reduces mortality [1].

Systematic review

The review used a very extensive search strategy for randomised and observational studies of critically ill adults or children and ICU physician staffing strategies. Staffing strategies were grouped into high intensity (mandatory consultations with intensive care physician, or closed care units where all care was directed by specialist intensive care physicians), or low intensity (no consultation with intensive care specialist or only elective consultation). Outcomes sought were hospital and ICU mortality and length of stay. Data extraction from reviewed studies was by intensive care physicians with formal training in clinical epidemiology.

Results

The final selection was of 26 studies, 16 reporting hospital mortality, 14 ICU mortality, 13 hospital length of stay and 18 ICU length of stay. All were observational studies, seven with concurrent and 19 with historical controls. Most studies were from North America. The number of ICUs studied was one in 20 studies and more than one (up to 42) in six. Twenty-five of the studies compared high intensity with low intensity physician staffing.

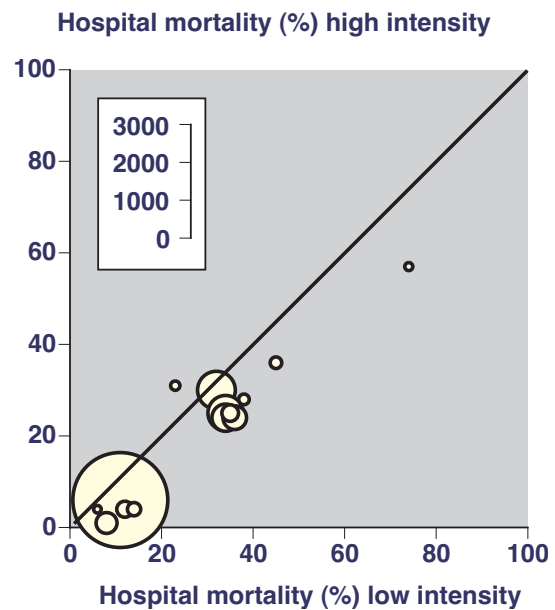
Hospital mortality

Results for hospital mortality are shown in Figure 1, where 16 of 17 studies showed a decrease in hospital mortality rate for ICU patients with high intensity physician staffing. In 10 studies the reduction was statistically significant. Overall 16% (859/5294) of patients died with high intensity staffing compared with 27% (943/3496) with low intensity staffing. The relative risk was 0.7 (0.6 to 0.8). The number needed to treat to prevent one additional death by using high rather than low ICU physician staffing was 9 (95% confidence interval 8 to 11).

ICU mortality

Results for ICU mortality are shown in Figure 2, where 14 of 15 studies showed a decrease in ICU mortality rate for ICU patients with high intensity physician staffing. In nine studies the reduction was statistically significant. Overall 10% (593/5703) of patients died with high intensity staffing compared with 14% (824/6077) with low intensity staffing. The relative risk was 0.6 (0.5 to 0.8). The number needed to treat to prevent one additional death by using high rather than low ICU physician staffing was 32 (95% confidence interval 23 to 50).

Figure 1: Effect of intensity of physician staffing on hospital mortality of critically ill patients



Hospital length of stay

Ten of 13 studies reported a reduction in hospital length of stay with high intensity physician staffing. In six studies the reduction was statistically significant. Overall, the weighted mean length of hospital stay in 5,083 patients in ICUs with high-intensity was 13.4 days, and in 3,383 patients in ICUs with low intensity staffing it was 15.4 days.

ICU length of stay

Fourteen of 18 studies reported a reduction in ICU length of stay with high intensity physician staffing. In 11 studies the reduction was statistically significant. Overall, the weighted mean length of ICU stay in 7,654 patients in ICUs with high-intensity was 4.4 days, and in 5,865 patients in ICUs with low intensity staffing it was 4.9 days.

Comment

The results were consistent. High intensity physician staffing in ICUs resulted in lower mortality and shorter hospital and ICU stays. That should reassure patients and professionals in the UK, because an Audit Commission survey in 1999 reported that high intensity physician staffing was the norm in at least 80% of ICUs in England and Wales.

That doesn't make it less interesting or important. As well as confirming other studies showing that more intensive staffing produces higher quality of care, this is ideal fodder for health economists to examine the cost-effectiveness. Saving half an ICU bed-day and two hospital days for each critically ill patient has major implications in cost and efficiency.

References:

- 1 PJ Pronovost et al. Physician staffing patterns and clinical outcomes in critically ill patients. *JAMA* 2002 288: 2151-2162.

SMOKING, COFFEE, AND PARKINSON'S DISEASE

Healthy living messages are usually relatively simple, and involve not smoking, eating fruit and vegetables, taking exercise and perhaps the odd glass of wine. That message does for heart disease, and cancer, and bone density and a raft of other things. It all gets more difficult when some of those lifestyle elements thought not to be good for us are actually shown to have some benefits. An example is the association between smoking and coffee drinking and the risk of Parkinson's disease [1].

Systematic review

An extensive search of several databases sought to identify studies associating smoking, coffee and Parkinson's disease. For inclusion studies had to have a case-control or cohort design, present original data, have Parkinson's disease diagnosed by a physician as the outcome, and attempt to ascertain exposure before the diagnosis.

Cigarette smoking

The 44 case-control studies involved 6,814 cases and 11,791 controls. Controls were often friends or relatives, patients with other diseases, or community controls, or a combination of these. The four cohort studies involved 409 cases in a total cohort size of just under 190,000.

Compared with never having smoked, cigarette smoking reduced the risk of developing Parkinson's disease (Table 1). There was a greater reduction for current smokers than for all smokers or past smokers. The magnitude of the risk reduction was similar for case-control and cohort studies. Each additional 10 pack years smoked was associated with a risk reduction of about 15%.

Coffee drinking

The eight case-control studies involved 1,440 cases and 4,016 controls. The four cohort studies involved 321 cases in a total cohort size of just under 190,000.

Compared with people who did not drink coffee, drinking coffee reduced the risk of developing Parkinson's disease (Table 1). The magnitude of the reduction was the same in case-control and cohort studies, and studies that adjusted for smoking. The evidence concerning the effect of the amount of coffee was mixed, though the authors estimated a risk reduction of 10% for each additional cup of coffee per day.

Comment

The results of this meta-analysis suggest that current smokers have a 60% lower risk of Parkinson's disease and coffee drinkers a 30% lower risk. The results were consistent across study design and geographical setting. Smokers who drink a lot of coffee will be given succour by these findings, but not for long.

First, Parkinson's disease occurs in only 1 in 200 of the elderly population, and 1 in 1,000 of the adult population. With cigarette smoking, the balance of risk is still negative, taking increased risks of cancer, and heart and respiratory disease into account.

Second, the association found in this meta-analysis does not prove that there is a cause and effect. There may be, but other possibilities exist and there is an interesting discussion about them in this paper. For instance, the diagnosis of Parkinson's disease could be more frequently omitted from death certificates and medical records of smokers (information bias). Another explanation may be that there is an increased mortality of younger smokers from causes other than Parkinson's disease (selection bias). Or again, smokers and sufferers of Parkinson's disease may share common genetic or environmental causes of which we are presently unaware (confounding). Perhaps patients with subclinical Parkinson's disease are less likely to start smoking or more likely to stop.

The authors of the paper argue persuasively against these possibilities, and suggest that smoking might protect against Parkinson's disease. We need to watch this space.

References:

- 1 MA Hernán et al. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Annals of Neurology* 2002 52: 276-284.

Table 1: Summary of results on smoking and coffee drinking and risk of Parkinson's disease

Status	Type of study	Number of studies	Relative risk (95% CI)
Ever smoked	All studies	45	0.58 (0.54 to 0.63)
	Case-control	41	0.59 (0.55 to 0.65)
	Cohort	4	0.52 (0.42 to 0.64)
Past smokers	All studies	16	0.80 (0.69 to 0.93)
Current smokers	All studies	18	0.39 (0.32 to 0.47)
Coffee drinker	All studies	12	0.69 (0.59 to 0.80)
	Case-control	8	0.66 (0.52 to 0.83)
	Cohort	4	0.70 (0.56 to 0.88)
Relative risk is by random effects model			

PREVENTING HYPERTENSION

Bandolier used to say about itself that it was not a destination, but a signpost for good evidence. That is still true, but sometimes it likes to point out where collections of good evidence can be found. Advice about the primary prevention of hypertension [1] is one such collection, impossible to summarise, but an invaluable tool to remind ourselves that raised blood pressure is frequently preventable if individuals do some simple things.

Benefits of living well

The Framingham study suggested that if we lived for a very long time, then hypertension will get about 90% of us, and about one person in two over the age of 60 years has hypertension. But hypertension is just one of a number of modifiable lifestyle factors that affect risk. *Bandolier's* Internet healthy living pages have collected studies that link healthy living with longer life in British men and American women.

Large cohort studies in over 350,000 young and middle-aged men and women have indicated people with low cardiovascular risk factors (serum cholesterol below 5.2 mmol/L, BP below 120/80 mmHg, no current cigarette smoking) have 70-85% lower mortality from cardiovascular disease and 40-60% lower mortality from all causes compared with those who have one of these three risk factors. This translates into an additional 6-10 years of life.

Strategies for primary prevention

The document recommends two. One is a population-based strategy to try and reduce the average blood pressure. Table 1 shows the benefits of small blood pressure reductions in the population.

The second strategy is a more intensive targeted approach aimed at achieving greater reduction in blood pressure in

Reduction in BP mmHg	Percent reduction in		
	Stroke	CHD	Total
2	6	4	3
3	8	5	4
5	14	9	7

those most likely to develop hypertension. High risk groups include those with a high normal blood pressure, with a family history of hypertension, of black ancestry, who are overweight, have a sedentary lifestyle, who have too much sodium or too little potassium in their diet, or who drink too much.

Documented efficacy

There are a number of interventions with well-documented efficacy in lowering blood pressure. They are simple to list, as in the box. They are more difficult to deliver, especially if

Lifestyle modifications for primary prevention of hypertension

- 1 Maintain normal body weight for adults (body mass index 18.5 to 24.9 kg/sq metre)
- 2 Reduce dietary sodium intake to no more than 100 mmol per day (about six grams of sodium chloride or 2.4 grams of sodium per day)
- 3 Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week)
- 4 Limit daily alcohol consumption to no more than 30 mL ethanol for men and no more than 15 mL for women and lighter weight persons [20 mL ethanol is equivalent to a pint and a half of beer, half a bottle of wine, or 60 mL of average strength spirits]
- 5 Maintain adequate intake of dietary potassium (more than 90 mmol or 3.5 grams per day)
- 6 Have a diet rich in fruits and vegetables and in low-fat dairy products with a reduced content of saturated and total fat

low sodium, high potassium foods are more expensive than those low in potassium but rich in salt, sugar, or fat.

Comment

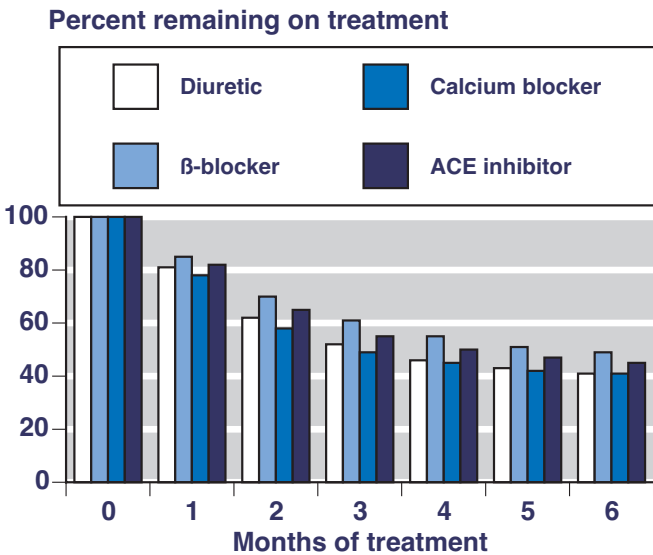
This document is well written, and thorough. It is not a scientific paper filled with statistics that stick for a moment, but a treatise filled with words and concepts that stick for a long time. The numbers included are there to illuminate and emphasise the importance of what is being related.

Bandolier often finds blood pressure a bit boring, but it is anything but boring for people starting new antihypertensive treatments. It is rarely pleasant, which is why so many change their medicines in the first few months (Figure 1).

References:

- 1 PK Whelton et al. Primary prevention of hypertension. Clinical and public health advisory from the National High Blood Pressure Education Program. JAMA 2002 288: 1882-1888.

Figure 1: Newly-treated antihypertensives



PROFIT AND HAEMODIALYSIS

Bandolier 102 examined an intriguing review from North America looking at the profit motive on healthcare and mortality. It concluded that there was a higher risk of death in for-profit than in not-for-profit hospitals. A new review of haemodialysis centres comes to the same conclusion [1].

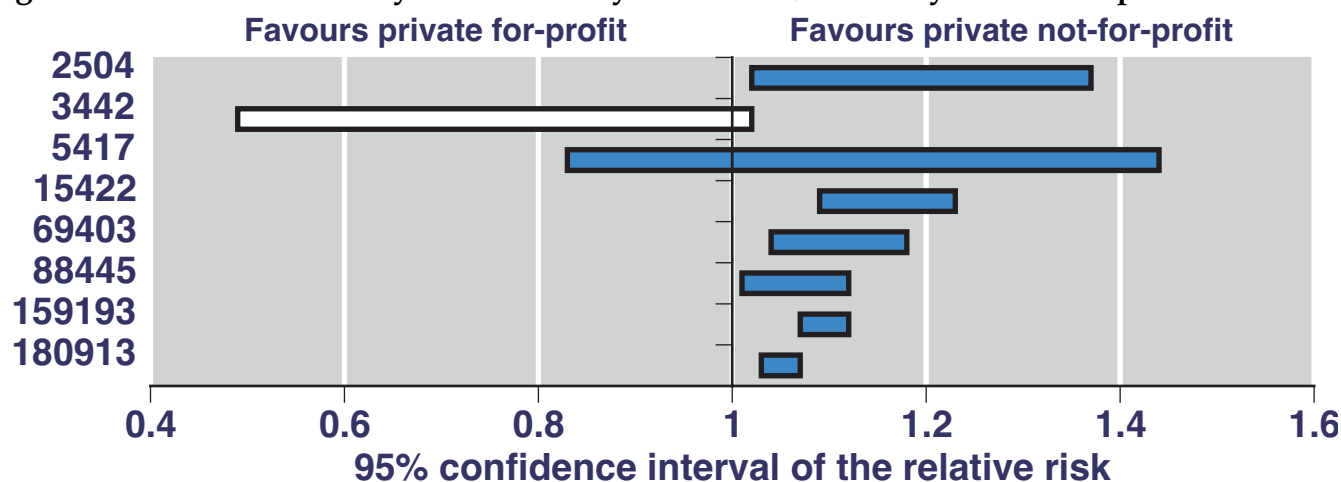
Review

The review is part of a larger study exploring the effects of the profit motive in healthcare. A complex search strategy examined 11 databases for studies examining mortality in haemodialysis patients in private centres run for profit, and private centres not run for profit. Both observational and randomised studies were looked for. Mortality, types of patients, and adjustment for potential confounding criteria were among information extracted from the studies.

Results

Seven publications reported eight observational studies, with 12 more that required additional information from authors but might eventually be eligible. The eight included studies had more than 500,000 patient years of information, with a follow up for individual patients between seven months and three to six years. All but one of the studies collected data in the 1990s, while the other collected data from 1973 to 1982.

Figure 1: Profit and mortality in haemodialysis centres (ranked by number of patients studied)



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Six of the eight studies, including the five largest studies, showed a statistically significant increase in mortality in for-profit haemodialysis centres (Figure 1). The only study with a point estimate of the relative risk in favour of for-profit centres was a small study performed over 20 years ago. The overall relative risk of death associated with for-profit haemodialysis centres was 1.09 (1.05 to 1.12).

Comment

The potential impact of this finding on the United States was significant. Using a conservative estimate that 20% receiving haemodialysis care die every year, and that 75% receive care in private for-profit centres, the authors estimate that 2,500 fewer lives would be lost (95% confidence interval 1,200 to 4,000) if private not-for-profit centres were used.

Perhaps the larger point is that if the funding is relatively fixed, then profit means running a system with less resource, especially the number and quality of the human resource. It doesn't work.

References:

- 1 PJ Devereaux et al. Comparison of mortality between private for-profit and private not-for-profit hemodialysis centers. A systematic review and meta-analysis. JAMA 2002 288: 2449-2457.